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The Human Dopamine D2 Receptor Gene Is Located on Chromosome 11 at q22-q23 and Identifies a *Taq*I RFLP

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Summary

Human dopaminergic neurons are involved in the control of hormone secretion, voluntary movement, and emotional behavior. Mediating these effects are the dopamine D_1 and D_2 receptors. These macromolecules belong to a large family of related sequences known as the G protein–coupled receptors. The D_2 receptors have been of special interest because they bind, with high affinity and specificity, many of the commonly prescribed antipsychotic drugs. We previously isolated a full-length cDNA clone of the rat D_2 receptor. When a chromosome mapping panel was probed with the rat D_2 receptor cDNA a 15-kb *Eco*RI restriction fragment was identified and localized to human chromosome 11. The rat cDNA was also used to clone a human genomic fragment, λhD2G1, which contains the last coding exon of the D_2 receptor gene (DRD2) and 16.5 kb of 3′ flanking sequence. Hybridization of λhD2G1 to a chromosome 11 regional mapping panel localized DRD2 to 11q. In situ hybridization of λhD2G1 to metaphase chromosomes refined this assignment to the q22-q23 junction of chromosome 11. A search for RFLPs associated with D2DR identified a frequent two-allele *Taq*I RFLP.

Introduction

Dopamine is an important neurotransmitter in the mammalian central nervous system. Acting through the nigrostriatal, tuberoinfundibular, and mesolimbic and mesocortical tracts, it is involved with the initiation and execution of movement, the regulation of peptide secretion from the pituitary, and emotional stability. Mediating these diverse effects of dopamine are two types of receptor, D_1 and D_2, which are distinguished by their ligand specificities and their effects on G protein–mediated second-messenger systems (Hess and Creese 1987; Vallar and Meldolesi 1989). The D_2 receptors have been further differentiated into postsynaptic and somatodendritic autoreceptors (Carlsson 1975; Groves et al. 1975).

The D_2 dopamine receptors are of interest for several reasons. Many clinically important antipsychotic drugs display high affinities for these receptors (Seeman and Lee 1975; Creese et al. 1976; Peroutka and Snyder 1980); their densities are altered in some neurological diseases (Seeman et al. 1984); prolactin secretion from lactotrophs is inhibited by D_2 receptor stimulation (Weiner and Ganong 1978); and these receptors have been implicated in the etiology of movement disorders (Lee et al. 1978), drug abuse (Barnes 1988), and tumors of the pituitary (Lachelin et al. 1977; Weiner et al. 1984). In spite of progress made in understanding the pharmacology and neurophysiology of the dopamine D_2 receptors, the relationship between their function, gene expression, and human disease remains unclear. We have initiated a study to better understand the human D_2 dopamine receptors at the molecular level. Here we present evidence that in the human genome the dopamine D_2 receptor gene (DRD2) is located on chromosome 11 at the q22–23 junction and that it identifies a *Taq*I RFLP.

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Material and Methods

Material

Chemical reagents were obtained from Sigma, except for formamide, which was manufactured by Boehringer Mannheim. DNA-modifying enzymes were purchased from Boehringer Mannheim, New England Biolabs, and Bethesda Research Laboratories. The Sequenase DNA sequencing kit was obtained from U.S. Biochemical Corporation. Radionucleotides, intensifying screens, hybridization membranes, and Colony/Plaque Screen filters were from New England Nuclear (DuPont). Nitrocellulose was purchased from Schleicher and Schuell. Geneclean is a product of Bio101, Inc.

Cloning of the Dopamine D_2 Receptor Gene Locus DRD2

A human genomic library (Clontech), prepared in EMBL3 with DNA from a normal male donor, was screened on duplicate nylon filters with the rat dopamine D_2 receptor cDNA as probe. The *Eco*RI/*Pst*I fragment of the rat cDNA was purified from an agarose gel by Geneclean and was nick-translated. The nylon filters were treated according to the manufacturer's specifications and hybridized with the probe, at 2×10^5 cpm/ml, in 50% formamide, 1 M NaCl, 1% SDS, and 100 μg yeast RNA/ml at 37°C. The filters were washed in 2 × SSC (1 × SSC = 150 mM NaCl/15 mM sodium citrate, pH 7.0), 0.1% SDS at 55°C and were autoradiographed overnight with one intensifying screen at −70°C. One genomic clone was identified by the rat cDNA probe. Its DNA was prepared, and the clone was mapped with restriction enzymes and partially sequenced in M13 phage vectors by using the Sequenase chain termination system.

Southern Blots and Chromosomal Mapping Panels

Genomic DNA for the chromosome mapping panel was prepared from parental and somatic cell hybrids—IMR91 (human), B82 (mouse), 1102 (hamster), CF84–2/8, CF84–4/8, CF84–5/8, CF84–7/8, CF84–20/8, CF84–21/5, CF84–25/8, CF84–27/8, CF84–34/9, CF84–35/8, CF84–39/5, and CF-11/4—according to a method described elsewhere (Boyd et al. 1988). All hybrid cell lines were mouse × human, except CF-11/4, which was hamster × human. Five micrograms *Eco*RI-digested DNA from each cell line was electrophoresed on 0.7% agarose, blotted to nylon, and probed with either the nick-translated coding sequence of the rat dopamine D_2 receptor cDNA or the entire human genomic clone (λhD2G1). Hybridizations with the rat cDNA were performed at 37°C for 72 h in 50% formamide, 1 M NaCl, 10 × Denhardt's (0.2% ficoll, 0.2% polyvinylpyrrolidone, 0.2% BSA fraction V), 100 mM Tris-HCl pH 7.4, 1 mm EDTA, 100 μg sheared, sonicated and denatured salmon sperm DNA/ml, 100 μg yeast/ml RNA, 0.1% sodium pyrophosphate. Hybridizations with the human genomic clone were performed in 5 × SSC, 1 × Denhardt's, 20 mM sodium phosphate pH 6.5, 10% dextran sulfate, 250 μg boiled and sonicated human placental DNA/ml, 250 μg boiled and sonicated salmon sperm DNA/ml, and 50% formamide at 42°C. The filter was washed in 0.1 × SSC/0.1% SDS at 55°C and was exposed to X-ray film with an intensifying screen for 4–6 d at −70°C. For the regional mapping of the human D_2 receptor gene, high-molecular-weight DNA was prepared from five somatic cell hybrid lines, each carrying a different rearrangement in chromosome 11. The cell lines used were MC-1, TGD51–1, J1–11, J1–44, and R28-4D. Their karyotypes have been described elsewhere (Maslen et al. 1988). Five micrograms *Taq*I-digested genomic DNA from each cell line was electrophoresed on 0.7% agarose, Southern blotted to nylon, and incubated with nick-translated λhD2G1 at 42°C. The filter was washed in 0.1 × SSC/0.1% SDS at 55°C and was exposed to film as described above. The λhD2G1 1.6-kb *Bam*HI fragment was isolated from a 0.7% agarose gel by using Geneclean. The purified fragment was converted into probe by nick-translation. The hybridization and washing conditions were the same as for the chromosome mapping panel. For the RFLP analysis genomic leukocyte DNA was digested with 31 restriction enzymes, electrophoresed, Southern blotted to nylon, and probed with the entire λhD2G1 clone. Hybridization was performed at 42°C, and washing was in 0.1 × SSC/0.1% SDS. Allelic frequencies were calculated for 18 unrelated individuals.

In Situ Hybridization

The entire human genomic clone (λhD2G1) was labeled with [^{3}H]-dTTP and [^{3}H]-dCTP to a specific activity of 3×10^7 dpm/μg. In situ hybridization was carried out on normal male metaphase chromosomes fixed to microscope slides according to the technique of Harper and Saunders (1981). Chromosomes were treated with RNAse for 1 h, were denatured in 70% formamide, 2 × SSC at 70°C for 2 min, and then were immersed in 70%, 80%, and 95% EtOH for 1 min each. Hybridization was performed in 50% formamide, 2 × SSCP, 10% dextran sulfate, and 100 μg human genomic DNA/ml for 14 h at 37°C. The slides were washed three times in 50% formamide plus 2 × SSC at 40°C for 3 min, by five washes in 2 × SSC for 2 min and dehydration by a series of 70%, 80%, and 90% alcohol washes. Kodak autoradiographic NTB-2 liquid emulsion was applied to the slides, and exposure was for 4–6 d at 4°C. The slides were developed and R-banded by a modification of the technique of Schweizer (1980). Silver grains were analyzed over fluorescent R-banded preparations by a double-illuminated system (Sawin et al. 1978). The χ^2 test was used to determine the significance of hybridization to chromosomes. Expected values for random distribution of hybridization events were determined for each chromosome according to a method described elsewhere (Jahnwar et al. 1983).

Results

DRD2 Is Localized to Human Chromosome 11

A chromosome mapping panel was used to assign the dopamine D2 receptor gene to human chromosome 11. The coding portion of the rat dopamine D2 receptor cDNA (Bunzow et al. 1988) was nick-translated and was used to probe a Southern blot of *Eco*RI-digested genomic DNAs prepared from 12 rodent-human somatic cell hybrids (Boyd et al. 1988). Under conditions of moderate stringency four human-specific genomic fragments of 4.1, 5.8, 8.0, and 15 kb hybridized with the probe (fig. 1). Because of the probe's hybridization to rodent genomic sequences with sizes similar to those of the three smallest human *Eco*RI fragments, only the presence of the 15-kb fragment could be clearly distinguished in the hybrid cell DNA. Four cell lines—CF84–7/8, 25/8, 27/8, and 34/9 (fig. 1, lanes 6, 9, 10, and 11, respectively)—gave strong signals, and one, CF84–20/8 (fig. 1, lane 7), gave a weak but detectable signal at 15 kb with the rat cDNA probe (see below). The discordancy analysis of these data correlated the presence of the 15-kb fragment with chromosome 11 (table 1).

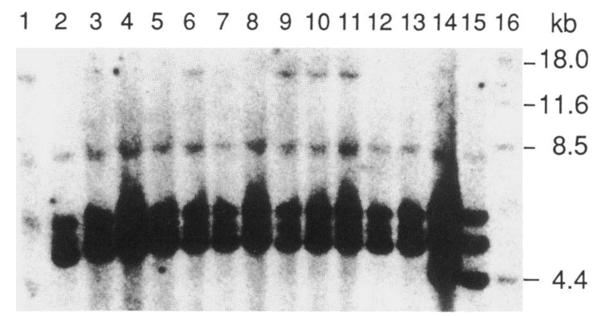

Figure 1 Chromosome mapping panel. Genomic DNA prepared from parental and somatic cell hybrid lines was digested with *Eco*RI, was Southern blotted, and was probed with nick-translated rat D2 cDNA. The cell lines analyzed were human IMR91 (lane 1), parental mouse B82 (lane 2), CF84–2/8 (lane 3), CF84–4/8 (lane 4), CF84–5/8 (lane 5), CF84–7/8 (lane 6), CF84–20/8 (lane 7), CF84–21/5 (lane 8), CF84–25/8 (lane 9), CF84–27/8 (lane 10), CF84–34/9 (lane 11), CF84–35/8 (lane 12), CF84–39/5 (lane 13), CF-11/4 (lane 14), hamster parental cell line 1102 (lane 15), and molecular-weight standards (lane 16). All hybrid cell lines are mouse × human, except lane 14, which is hamster × human.

Partial Cloning of DRD2

To begin the molecular analysis of DRD2 a library prepared from normal male genomic DNA was screened with the rat cDNA, under moderately stringent conditions. One clone, λhD2G1, was identified and found to contain an 18-kb insert. *Bam*HI digestion of λhD2G1 generated several fragments, including one of 1.6-kb which hybridized with the rat probe. This fragment was subcloned into M13mp19 and was completely sequenced in both orientations (data not shown). By comparison of the rat and human genomic sequences it was possible to identify the entire 3′ coding exon of the human dopamine D2 receptor gene plus a portion of its 5′ intronic and 3′ noncoding sequences. When used to reprobe the rodent-human hybrid cell panel, λhD2G1 gave a strong signal at 15 kb in the same cell lines (including CF/84–20/8) as did the rat cDNA. This human genomic clone was then used to regionally map the receptor gene on chromosome 11.

Assignment of DRD2 to the Long Arm of Human Chromosome 11

In order to regionally map the D2 receptor gene on chromosome 11, five cell lines, each carrying a different rearrangement in chromosome 11, were analyzed (Maslen et al. 1988). The *Taq*I-digested rodent-human hybrid cell DNA was subjected to a Southern analysis using λhD2G1 as probe (fig. 2, *left*). A human-specific fragment of 6.6 kb was identified in the cell lines MC-1 (lane 1) and TGD51–1 (lane 2); two *Taq*I fragments of 2.9 and 3.6 kb were present in J1–44 (lane 4) and R28–4D; and no signal was detected in J1–11 (lane 3). These results, summarized in figure 2, *right,* localized the human D2 dopamine receptor gene to the q22-q23 region of 11. This experiment also provided the first evidence of a *Taq*I RFLP associated with the human dopamine D2 receptor gene (see below).

In Situ Hybridization

As an independent means of confirming the chromosomal localization of DRD2, in situ hybridization was performed on normal male metaphase chromosomes (fig. 3). One hundred metaphase spreads were

Table 1

Discordancy Analysis of the Human 15-kb Genomic *EcoRI* Fragment

Human Chromosome	Concordant +/+	Concordant −/−	Discordant +/−	Discordant −/+	% Discordancy
1	...	5	2	5	58
2	2	4	3	3	50
3	2	3	3	4	58
4	4	4	1	3	33
5	2	4	2	2	40
6	4	3	1	4	42
7	2	2	2	5	64
8	5	2	...	5	42
9	...	6	5	1	50
10	2	5	3	2	42
11	5	6	...	...	0
12	4	4	1	3	33
13	1	5	4	2	50
14	2	3	3	4	58
15	...	4	5	3	67
16	1	5	4	2	50
17	5	1	...	6	50
18	2	5	3	2	42
19	1	4	3	3	54
20	4	4	1	3	33
21	3	5	2	2	33
22	2	5	3	2	42
X	1	5	4	2	50
Y	...	5	5	1	54

NOTE.—Concordant (+/+ or −/−) and discordant (+/− or −/+) segregation of the 15-kb fragment was determined for each of the 12 somatic cell hybrid lines analyzed (fig. 1). +/− Indicates that the 15-kb band was detected but that the particular chromosome was not present, wherease −/+ indicates that the fragment was not detected but that the chromosome was present. The % discordancy was calculated for each chromosome by dividing the number of hybrid cell lines in which the probe did not segregate by the total number hybrid cell lines scored.

scored for silver grains, with 199 grains counted over chromosomes (fig. 4). Of the 100 cells analyzed, 18% had grains on chromosome 11 at the junction of bands q22-q23 (9% of total grains). This represented a significant deviation ($P < .001$) from the expected number of grains on 11q. A second region of hybridization was also observed over 7p; however, this level of signal was not statistically significant.

λhD2G1 Recognizes a TaqI RFLP

A search for RFLPs recognized by λhD2G1 was conducted. Of the 31 restriction enzymes tested (data not shown), only *TaqI* generated an RFLP with λhD2G1 as probe. In order to characterize this RFLP, a Southern analysis was performed. *TaqI*-digested human DNA prepared from 18 unrelated individuals was probed with λhD2G1 (fig. 5). Allele A1 was identified by λhD2G1 hybridization to a 6.6-kb *TaqI* fragment (lanes 4, 11, 13, 14, 17, and 18), and allele A2 was characterized by the two *TaqI* fragments of 2.9 and 3.7 kb (lanes 1–10 and 12–16). Constant bands at 2.3 and 10.5 kb were observed in all individuals. Allelic frequencies for A1 and A2 were measured in 43 unrelated Caucasians and were calculated to be 24% for A1 and 76% for A2. Codominant Mendelian inheritance was observed in three informative families with a total of 39 children (data not shown).

Discussion

The results obtained from the hybrid cell panels and from in situ hybridization localize the human dopamine

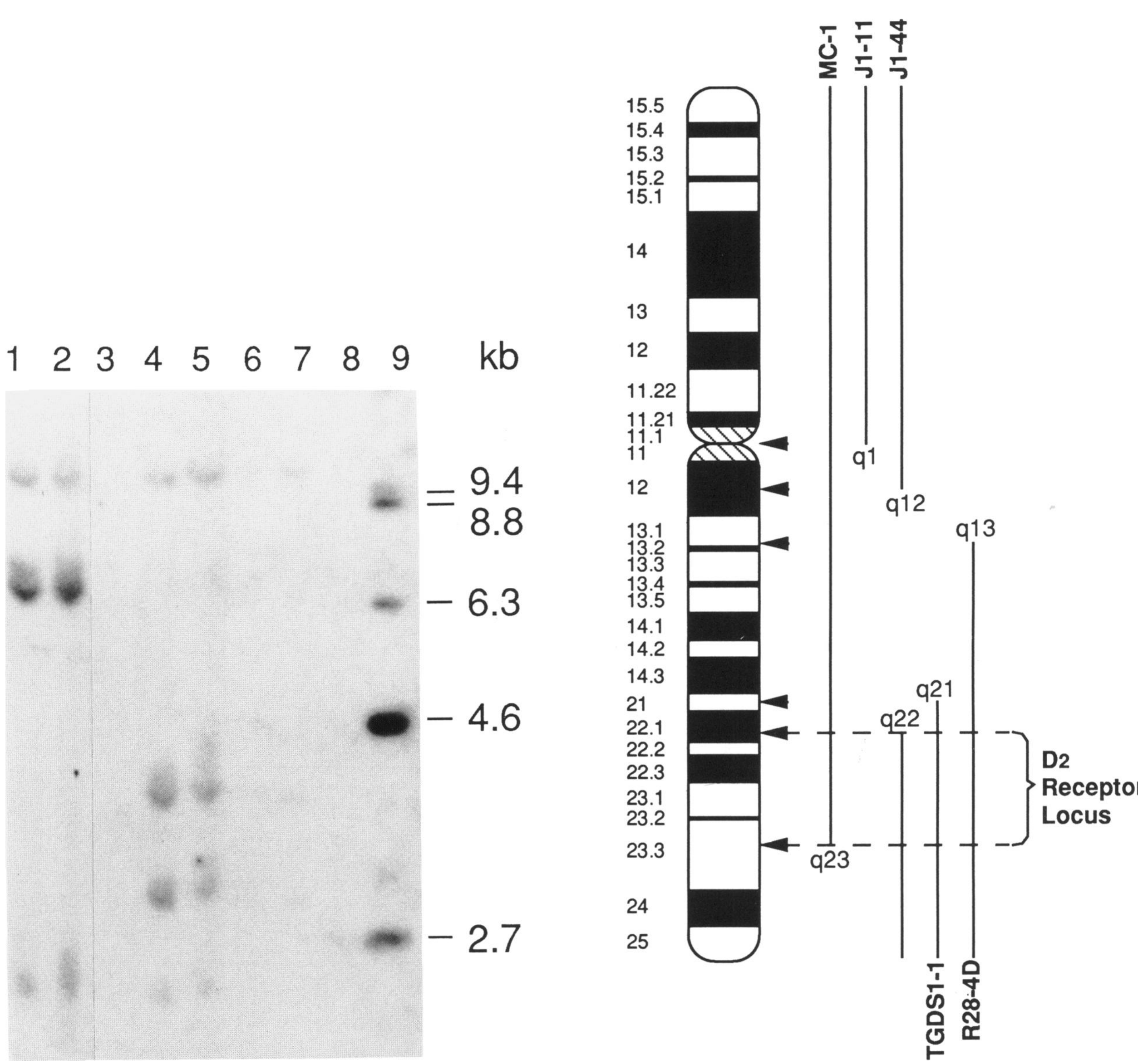

Figure 2 Regional mapping of DRD2 to 11q. *Left,* Southern blot of *Taq*I-digested DNAs prepared from five cell lines, each with a different rearranged human chromosome 11, was hybridized with λhD2G1. The DNAs were MC-1 (lane 1), TGD51-1 (lane 2), JL-11 (lane 3), J1-44 (lane 4), R28-4D (lane 5), 0.5 and 1.0 μg human genomic DNA (lanes 6 and 7, respectively), 5 μg mouse genomic DNA (lane 8), and molecular-weight standards (lane 9). *Right,* Ideogram of chromosome 11 at the 550-band stage (Harnden and Klinger 1985), showing the regions present in each hybrid cell line and the approximate location of DRD2 at 11q22-q23.

D2 receptor gene (DRD2) to the q22-q23 region of chromosome 11. Recently, the gene for ataxia telangiectasia A (AT), a human autosomal recessive disorder, was assigned to this same region of chromosome 11 (Gatti et al. 1988). It is interesting that one symptom of AT is movement dysfunction—and, in view of the D2 receptor's involvement in controlling movement, it will be of interest to determine how closely these two loci are linked. Some of the genes which have been mapped to this region of 11q are are THY1, CD3, N-CAM, and apolipoproteins A1, C3, and A4.

That dopamine D2 receptors are involved in human psychoses has often been suggested, since many potent antipsychotic drugs have high affinities for these recep-

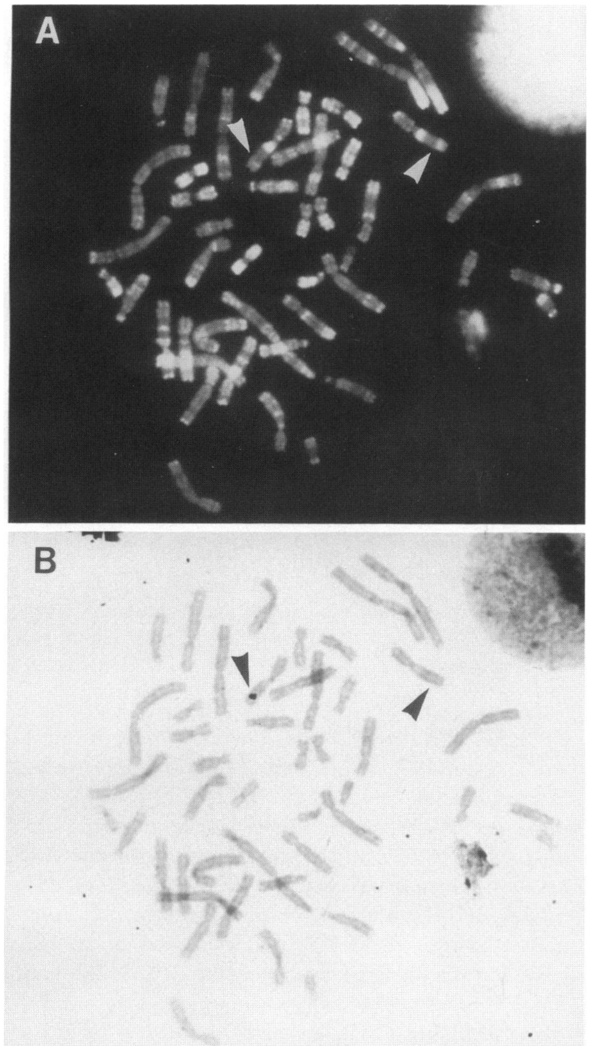

Figure 3 Metaphase chromosome spread from a normal male donor. The chromosomes were fluorescently R-banded (*A*) for identification, and the silver grains (arrowheads) associated with hybridization to λhD2G1 (*B*) were observed with standard Wright's staining.

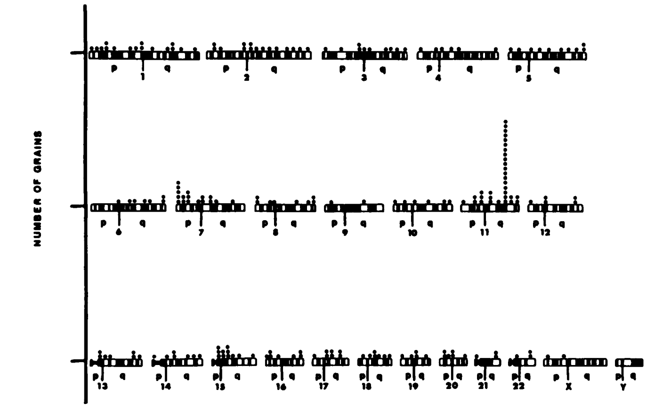

Figure 4 Distribution of silver grains over 100 metaphase spreads due to in situ hybridization of λhD2G1. Each dot represents one silver grain observed over the indicated region. The most significant hybridization was to the junction of 11q22-q23. Chromosomes are diagrammed at the 400-band stage.

tors (Seeman 1987). However, the most common psychotic disorder, schizophrenia, is clinically heterogeneous (Tomb 1988) and undoubtedly of complex etiology. It has been recognized for some time that schizophrenia tends to cluster in families, and recently an analysis of RFLP markers on chromosome 5 identified a dominant schizophrenia-susceptibility allele (Sherrington et al. 1988) in seven British and Icelandic families. In contrast, a study of a northern Swedish pedigree provided strong evidence against linkage of schizophrenia with markers on chromosome 5 (Kennedy et al. 1988). In view of the complex nature of this mental illness, these results are not surprising. We are currently investigating the linkage of DRD2 to both schizophrenia and other disorders in a number of different kindreds.

DRD2 is also interesting at the structural level. Unlike most genes that code for G protein–coupled receptors (O'Dowd et al. 1989), introns interrupt the sequence encoding the D_2 protein (D. K. Grandy et al., unpublished results). The complete characterization of the intron-exon organization of the human and rat dopamine D_2 receptor genes is currently in progress. Finally, when the cloning of the DRD2 locus is complete, the exact number of D_2 genes can be determined. All of our observations are consistent with the existence of a single dopamine D_2 receptor gene in man; however, this remains to be conclusively demonstrated. Determining the number of dopamine D_2 receptor genes will have important implications for studies of D_2 receptor subtypes.

In summary, our results indicate that the human D_2 dopamine receptor is encoded by a gene located at the q22-q23 junction of chromosome 11; that, unlike most other G protein–coupled receptor genes, the coding sequence is interrupted by introns; and that the dopamine D_2 receptor gene locus (DRD2) contains a frequent *Taq*I RFLP.

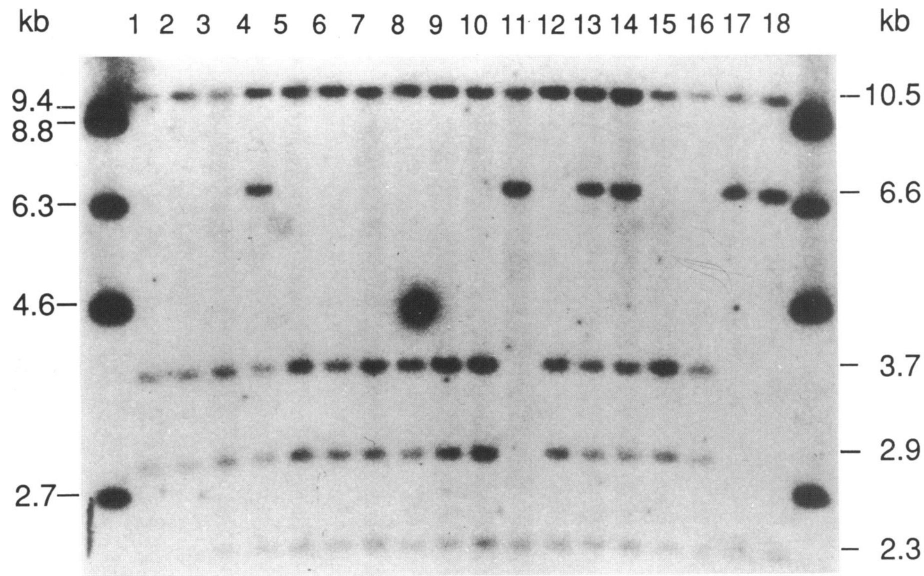

Figure 5 λhD2G1 identifies a *Taq*I RFLP. Eighteen unrelated individuals (lanes 1–18) were evaluated using λhD2G1 as the probe. The sizes (in kb) of the standards are indicated on the left. The sizes on the right correspond to the fragments which hybridized to the probe.

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